

What is claimed is:

1. A method for treating a subject suffering from a
5 condition associated with an extracellular zinc
sphingomyelinase activity which comprises administering
to the subject an amount of a zinc sphingomyelinase
inhibitor effective to decrease extracellular zinc
sphingomyelinase activity in the subject and thereby
10 treat the subject.
2. The method of claim 1, wherein the extracellular zinc
sphingomyelinase is present in the subject at a
15 concentration which is higher than that present in the
subject prior to the onset of the condition.
3. The method of claim 1, wherein the condition is an
20 atherosclerotic vascular disease, an inflammatory
disease, an infectious disease, an autoimmune disease,
or a demyelinating disease.
4. The method of claim 3, wherein the atherosclerotic
vascular disease is coronary artery disease, cerebral
25 vascular disease, peripheral vascular disease,
transplantation atherosclerosis, vein graft
atherosclerosis, or vaculitis-induced atherosclerosis.
5. The method of claim 3, wherein the demyelinating
30 disease is multiple sclerosis, progressive multifocal
leucoencephalopathy, Guillain-Barre syndrome,
Retrobulbar neuritis, acute rubella encephalitis,
chronic relapsing polyneuropathy, intravascular
lymphomatosis, Krabbe disease, globoid cell
35 leukodystrophy, subacute combined degeneration of the
spinal cord and brain, allergic encephalitis, murine
coronavirus, hepatitis virus infection, or Theiler's
murine encephalomyelitis.

6. The method of claim 1, wherein the zinc sphingomyelinase inhibitor comprises a peptide or polypeptide, a peptidomimetic compound, an organic compound, a nucleic acid, an inorganic compound, or an antibody or fragment thereof.
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7. The method of claim 6, wherein the inhibitor is an antibody capable of binding to and inactivating zinc sphingomyelinase.
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8. The method of claim 6, wherein the inhibitor is an antibody which comprises a monoclonal or a polyclonal antibody.
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9. The method of claim 1, wherein the inhibitor comprises a compound capable of competing with sphingomyelin for binding to naturally occurring zinc sphingomyelinase.
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10. The method of claim 1, wherein the inhibitor is a pseudoenzyme.
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11. The method of claim 1, wherein the administration comprises intralesional, intraperitoneal, intramuscular or intravenous injection; infusion; liposome-mediated delivery; topical, nasal, oral, anal, subcutaneous, vaginal, sublingual, intrathecal, urethral, transdermal, ocular or otic delivery.
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12. The method of claim 1, wherein the zinc sphingomyelinase inhibitor comprises a portion of a naturally occurring zinc sphingomyelinase.
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13. The method of claim 12, wherein the portion consists essentially of a sphingomyelin binding site of the sphingomyelinase.
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14. The method of claim 1, wherein the zinc

sphingomyelinase inhibitor is a compound having a structure which mimics the structure of a substrate of sphingomyelinase or the structure of a product of sphingomyelinase.

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15. The method of claim 14, wherein the substrate of sphingomyelinase is sphingomyelin.
16. The method of claim 14, wherein the product of sphingomyelinase is ceramide or choline phosphate.
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17. A method for determining whether a compound inhibits an activity of an extracellular zinc sphingomyelinase involving ceramide formation which comprises:
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- (a) contacting a sample containing the zinc sphingomyelinase under acidic pH conditions known to be associated with the activity of such zinc sphingomyelinase, with:
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- (i) a substrate of the zinc sphingomyelinase, and
- (ii) the compound being evaluated;
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- (b) measuring the concentration of ceramide in the sample from (a);
- (c) determining the amount of zinc sphingomyelinase activity in the sample based upon the concentration of ceramide measured in step (b); and
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- (d) comparing the amount of sphingomyelinase activity determined in step (c) with the amount of sphingomyelinase activity determined in the absence of the compound, so as to
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determine whether the compound inhibits the activity of zinc sphingomyelinase.

18. The method of claim 17, wherein the substrate comprises sphingomyelin or a derivative thereof or a lipoprotein.
19. The method of claim 18, wherein the substrate is detectably labeled.
20. The method of claim 19, wherein the detectable label comprises a radioisotope or a fluorophor.
21. The method of claim 18, wherein the lipoprotein comprises an oxidized lipoprotein, a phospholipase-A-II treated lipoprotein, an apolipoprotein-C-III-enriched population of lipoproteins, a lipoprotein obtained from an apolipoprotein-E knock-out mouse, or a sphingomyelin-enriched population of lipoproteins or emulsions thereof at neutral pH.
22. The method of claim 17, wherein steps (a) through (d) are repeated for multiple compounds.
23. A method for determining whether a compound inhibits an activity of an extracellular zinc sphingomyelinase involving ceramide formation which comprises:
 - (a) contacting a sample containing the zinc sphingomyelinase under neutral pH conditions known to be associated with the activity of such zinc sphingomyelinase, with:
 - (i) a substrate of the zinc sphingomyelinase, and
 - (ii) the compound being evaluated;

- (b) measuring the concentration of ceramide in the sample from (a);
- 5 (c) determining the amount of zinc sphingomyelinase activity in the sample based upon the concentration of ceramide measured in step (b); and
- 10 (d) comparing the amount of sphingomyelinase activity determined in step (c) with the amount of sphingomyelinase activity determined in the absence of the compound, so as to determine whether the compound inhibits the activity of zinc sphingomyelinase.
- 15 24. A method for screening a library of compounds to identify a compound capable of inhibiting an activity of zinc sphingomyelinase involving ceramide formation which comprises:
- 20 (a) contacting a zinc sphingomyelinase under acidic pH conditions known to be associated with the activity of such zinc sphingomyelinase, with:
- 25 (i) a substrate of sphingomyelinase, and
- (ii) a sample from a library of compounds being evaluated;
- 30 (b) measuring the concentration of ceramide in the sample from (a); and
- 35 (c) determining the amount of zinc sphingomyelinase activity in the sample based upon the concentration of ceramide measured in step (b); and

- 5 (d) comparing the amount of sphingomyelinase activity determined in step (c) with the amount of sphingomyelinase activity determined in the absence of the sample, so as to determine whether the sample inhibits the activity of zinc sphingomyelinase, and
- 10 (d) repeating steps (a) through (d) with limiting dilutions of the sample so as to identify the compound in the sample capable of inhibiting zinc sphingomyelinase.

25. A method for determining whether a subject is at increased risk for becoming afflicted with an increase
15 in the concentration of extracellular zinc sphingomyelinase activity in the subject, which comprises:

- 20 (a) obtaining a sample of a body fluid from the subject;
- (b) determining the amount of extracellular zinc sphingomyelinase activity in the body fluid sample, and
- 25 (c) comparing the amount of extracellular zinc sphingomyelinase activity determined in step (a) with the amounts of extracellular zinc sphingomyelinase activity determined for the
30 subject at earlier points in time, an increase in the amount of such activity indicating that the subject is at increased risk for such condition.

35 26. The method of claim 25, wherein the condition is an atherosclerotic vascular disease, an inflammatory disease, an infectious disease, an autoimmune disease,

or a demyelinating disease.

27. The method of claim 26, wherein the atherosclerotic
vascular disease is coronary artery disease, cerebral
5 vascular disease, peripheral vascular disease,
transplantation atherosclerosis, vein graft
atherosclerosis, or vaculitis-induced atherosclerosis.
28. The method of claim 26, wherein the demyelinating
10 disease is multiple sclerosis, progressive multifocal
leucoencephalopathy, Guillain-Barre syndrome,
Retrobulbar neuritis, acute rubella encephalitis,
chronic relapsing polyneuropathy, intravascular
lymphomatosis, Krabbe disease, globoid cell
15 leukodystrophy, subacute combined degeneration of the
spinal cord and brain, allergic encephalitis, murine
caronavirus, hepatitis virus infection, or Theiler's
murine encephalomyelitis.
- 20 29. The method of claim 25, wherein the body fluid is
plasma, blood, serum, interstitial fluid, cerebrospinal
fluid, joint fluid, tears, semen, urine, saliva, bile,
or amniotic fluid.
- 25 30. A method for determining whether a subject has
lipoproteins susceptible to extracellular zinc
sphingomyelinase activity and thus is at increased risk
for becoming afflicted with a condition associated with
extracellular zinc sphingomyelinase activity which
30 comprises:
- (a) obtaining a sample of a body fluid from the
subject;
 - 35 (b) isolating the lipoproteins present in the
sample;

- (c) contacting the isolated lipoproteins with zinc sphingomyelinase enzyme under acidic pH conditions known to be associated with the activity of such zinc sphingomyelinase;
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- (d) measuring the concentration of ceramide in step (c), thereby determining whether the subject has lipoproteins susceptible to extracellular zinc sphingomyelinase so as to
- 10 determine whether the subject is at increased risk for becoming afflicted with a condition associated with extracellular zinc sphingomyelinase activity.
- 15 31. The method of claim 30, wherein the condition is an atherosclerotic vascular disease, an inflammatory disease, an infectious disease, an autoimmune disease, or a demyelinating disease.
- 20 32. The method of claim 31, wherein the atherosclerotic vascular disease is coronary artery disease, cerebral vascular disease, peripheral vascular disease, transplantation atherosclerosis, vein graft atherosclerosis, or vaculitis-induced atherosclerosis.
- 25 33. The method of claim 31, wherein the demyelinating disease is multiple sclerosis.
- 30 34. The method of claim 30, wherein the body fluid is plasma, blood, serum, interstitial fluid, cerebrospinal fluid, joint fluid, tears, semen, urine, saliva, bile, or amniotic fluid.
- 35 35. A pharmaceutical composition comprising an amount of an inhibitor of an extracellular zinc sphingomyelinase effective to inhibit the activity of such zinc sphingomyelinase in a subject and a pharmaceutically

acceptable carrier.

36. The pharmaceutical composition of claim 35, wherein the carrier comprises a diluent.
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37. The pharmaceutical composition of claim 35, wherein the carrier further comprises an adjuvant, a liposome, a microencapsule, a polymer encapsulated cell, a biodegradable plastic or a retroviral vector.
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38. The pharmaceutical composition of claim 35, wherein the composition is in a form suitable for aerosol, intravenous, oral or topical administration.